Statistical Analysis Plan for Study M23-072

A Phase 4, Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, and Efficacy of the Concomitant Use of Ubrogepant for the Acute Treatment of Migraine in Subjects Taking Atogepant for the Preventive Treatment of Episodic Migraine

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Version 2.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for atogepant Study M23-072, A Phase 4, Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, and Efficacy of the Concomitant Use of Ubrogepant for the Acute Treatment of Migraine in Subjects Taking Atogepant for the Preventive Treatment of Episodic Migraine.

Study M23-072 is to evaluate the safety and tolerability of the concomitant use of ubrogepant 100 mg for the acute treatment of breakthrough migraine headache in subjects taking atogepant 60 mg once daily for preventive treatment of EM.

The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analysis.

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) or later under the LINUX operating system.

2.0 Study Design and Objectives

2.1 Objectives, Hypotheses and Estimands

The primary objective of this study is to evaluate the safety and tolerability of the concomitant use of ubrogepant 100 mg for the acute treatment of breakthrough migraine headache in subjects taking atogepant 60 mg once daily for preventive treatment of EM.

The exploratory objectives are:

- To evaluate the clinical benefit of the concomitant use of ubrogepant 100 mg, taken as needed, and atogepant 60 mg once daily in subjects with EM.
- To explore the efficacy of ubrogepant 100 mg, taken as needed, for the acute treatment of migraine in subjects taking atogepant 60 mg once daily for preventive treatment of EM.

The efficacy endpoints are exploratory in this study; therefore, no estimand attributes for efficacy endpoints will be provided.

2.2 Study Design Overview

This is a multicenter, open-label, Phase 4 study conducted in the United States (US) to evaluate the safety, tolerability, and efficacy of the concomitant use of ubrogepant 100 mg for the acute treatment of breakthrough migraine headache in subjects taking atogepant 60 mg once daily for preventive treatment of EM.

Subject participation will begin with up to a 1-week screening period. Subjects who continue to meet all entry criteria at baseline/Visit 2 (Day 1) will be assigned atogepant 60 mg once daily for the preventive treatment of migraine.

Screen failures are defined as subjects who consent to participate in the study, however, are not subsequently assigned to receive study drug. Rescreening of screen failures is permitted in certain situations, with permission from the Sponsor, however, subjects with clinically laboratory values at Visit 1 (including ALT or AST > 1 x ULN, total bilirubin > 1 or serum albumin < 2.8 g/dL) are not allowed to be rescreened.

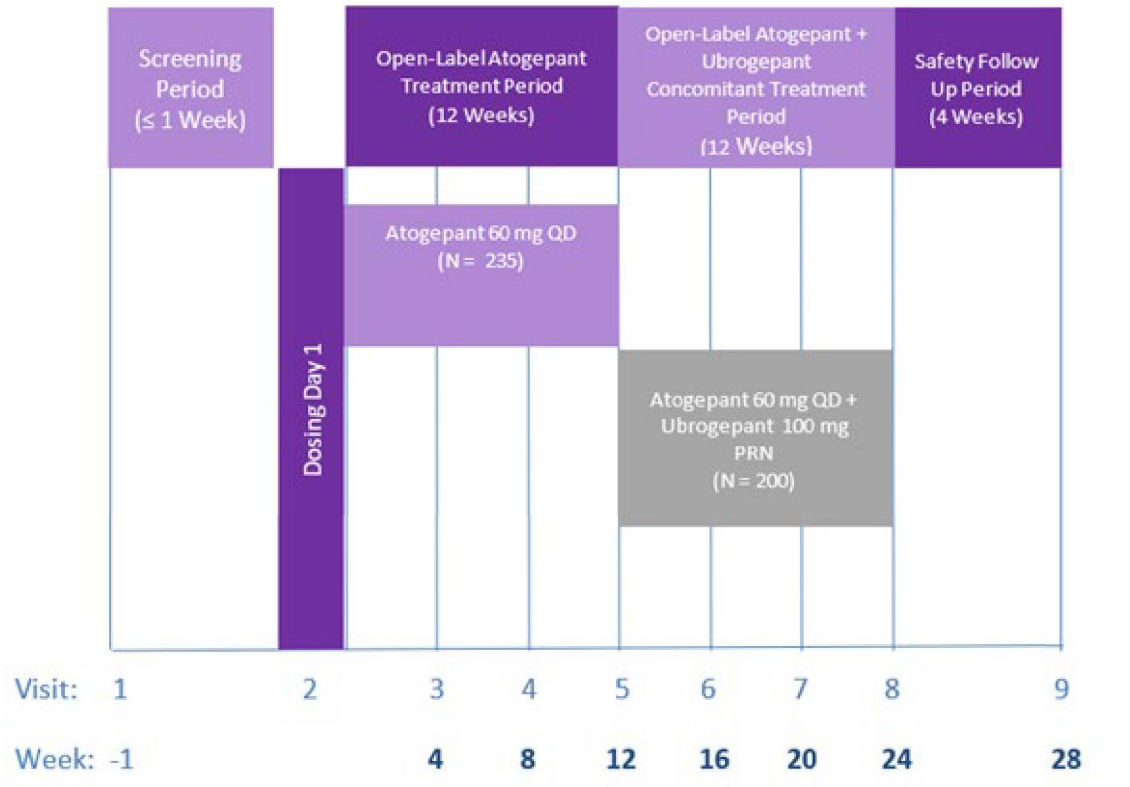
The open-label atogepant treatment period will last for 12 weeks (Visits 2-5). During this study period, subjects will use their usual medications for the acute treatment of breakthrough migraine headaches. At Visit 5, subjects who complete the open-label atogepant treatment period will continue into the open-label atogepant + ubrogepant concomitant use period which will last for an additional 12 weeks (Visits 5 to 8). During this study period, subjects will continue to take atogepant 60 mg once daily and will also be provided ubrogepant 100 mg to treat up to 8 breakthrough migraine headaches of any pain intensity per 4-week visit interval. For each breakthrough migraine, subjects will take a dose of ubrogepant 100 mg to treat their breakthrough migraine headache. If the migraine headache pain persists or returns, subjects may opt to take the second dose of ubrogepant 100 mg or their own medication starting 2 to 24 hours after the first dose of ubrogepant 100 mg was taken.

There will be a total of 9 scheduled clinic visits: Screening/Visit 1 (Week -1), Baseline/Visit 2 (Day 1), Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12), Visit 6 (Week 16), Visit 7 (Week 20), Visit 8/Early Termination (Week 24), and Visit 9/Safety Follow-up (Week 28). The total duration of study participation is 29 weeks. Total treatment duration is 24 weeks.

All subjects who take at least 1 dose of atogepant 60 mg will enter a safety follow-up period of 4 additional weeks after their last dose of study drug. All subjects, regardless of the number of doses of study drug which are self-administered, should complete Visits 8 and 9, unless the subject has withdrawn consent. An interim analysis that includes all safety and efficacy analyses is planned. Details are provided in Section 10.6.

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



2.3 Treatment Assignment and Blinding

Approximately 235 subjects will be enrolled to receive the following open-label treatment:

- Open-label atogepant treatment period: atogepant 60 mg once daily for 12 weeks (Day 1 to Week 12)
- Open-label atogepant and ubrogepant concomitant use treatment period: atogepant 60 mg once daily + ubrogepant 100 mg as needed to treat breakthrough migraine headache for 12 weeks (Week 12 to 24)

No randomization or stratification is required as this will be an open-label study.

All subjects will be assigned a unique identification number by the IRT at the Screening Visit. For subjects who rescreen, the screening number assigned by the IRT at the initial Screening Visit should be used.

2.4 Sample Size Determination

Approximately 235 subjects will be assigned to receive open-label atogepant 60 mg once daily for the preventive treatment of episodic migraine at Baseline/Visit 2 (Day 1). Based on historical data from previously completed clinical studies, it is assumed that 15% of subjects will discontinue from the study during the atogepant treatment period (Day 1 to Week 12). Therefore, approximately 200 subjects will be assigned to also receive ubrogepant 100 mg for the acute treatment of migraine starting at Visit 5 (Week 12).

This sample size will provide estimation for AEs of interest occurring in either the open-label atogepant treatment period (Day 1 to Week 12) or the open-label atogepant and ubrogepant concomitant use treatment period (Weeks 12 to 24) with a precision (defined as the half width of 95% confidence interval) of approximately ± 3% to 5%.

3.0 Endpoints

3.1 Primary Endpoint

The primary endpoint is to assess the safety endpoints, including adverse event (AE) monitoring, vital sign measurements, electrocardiogram (ECG) variables, clinical laboratory testing (hematology, chemistry, and urinalysis), and Columbia Suicide Severity Rating Scale (C-SSRS).

3.2 Exploratory Efficacy Endpoint(s)

- Change from baseline in mean monthly migraine days, headache days, and acute medication use days across Weeks 1 to 12, Weeks 13 to 24, and at each 4-week interval.

- Achievement of at least ≥ 25%, ≥ 50%, ≥ 75%, and 100% reduction in mean monthly migraine days across Weeks 1 to 12, Weeks 13 to 24, and at each 4-week interval.
- Percentages of migraine attacks treated with ubrogepant that result in pain freedom at 2 hours, pain relief at 2 hours, sustained pain freedom from 2 to 24 hours, and sustained pain relief from 2 to 24 hours across Weeks 13 to 24, and at each 4-week interval.
- Patient satisfaction with atogepant at Week 12 and Week 24.
- Patient satisfaction with ubrogepant, taken as needed, at Week 24.
- Patient satisfaction with the concomitant use of atogepant and ubrogepant (taken as needed) at Week 24.
- Change from baseline in the Headache Impact Test (HIT)-6 total score at Weeks 4, 8, 12, 16, 20, and 24.
- At least a 5-point improvement (decrease) from baseline in HIT-6 total score at Weeks 4, 8, 12, 16, 20, and 24.
- Patient Global Impression of Change (PGIC) of "much better" or "very much better" at Week 12 (atogepant) and Week 24 (atogepant + ubrogepant).
- Change from baseline in percent work time missed, percent impairment while working, percent overall impairment, and percent activity impairment due to migraine at Weeks 4, 8, 12, 16, 20, and 24 as assessed by the Work Productivity and Activity Impairment Questionnaire: Migraine (WPAI:MIGRAINE).
- Change from baseline in the Migraine-Specific Quality-of-Life Questionnaire (MSQ) v2.1 Role Function-Preventive domain score at Weeks 4, 8, 12, 16, 20, and 24.
- Change from baseline in the MSQ v2.1 Role Function-Restrictive domain score at Weeks 4, 8, 12, 16, 20, and 24.
- Change from baseline in the MSQ v2.1 Emotional Function domain score at Weeks 4, 8, 12, 16, 20, and 24.
- Change from baseline in the Patient Health Questionnaire (PHQ)-4 score at Weeks 4, 8, 12, 16, 20, and 24.

- Migraine Treatment Optimization Questionnaire (MTOQ)-6 score at Weeks 16, 20, and 24.

3.3 Safety Endpoint(s)

The safety parameters include including adverse event (AE) monitoring, vital sign measurements, electrocardiogram (ECG) variables, clinical laboratory testing (hematology, chemistry, and urinalysis), and Columbia Suicide Severity Rating Scale (C-SSRS). For clinical laboratory, vital sign, and ECG parameters, the last non-missing safety assessment before the first dose of treatment will be used as the baseline for all analyses of that safety parameter.

All AEs and other safety data will be presented in the listings at the subject level.

4.0 Analysis Populations

The modified intent-to-treat 1 (mITT1) population includes all enrolled subjects who received at least 1 dose of study drug, have a baseline assessment, and have at least 1 postbaseline assessment during the open-label atogepant treatment period. The modified intent-to-treat 2 (mITT2) population includes all enrolled subjects who received at least 1 dose of study drug, have a baseline assessment, and have at least 1 postbaseline assessment during the open-label atogepant + ubrogepant treatment period. The mITT1 or mITT2 populations will be used for all efficacy analyses.

The Safety Population 1 consists of all subjects who received at least 1 dose of study drug during the open-label atogepant treatment period. The Safety Population 2 consists of all subjects who received at least 1 dose of study drug during the open-label atogepant + ubrogepant treatment period. The Safety Population 1 or Safety Population 2 will be used for safety analyses.

5.0 Subject Disposition

Summaries will be provided for subjects in each of the following categories:

- Subjects who were screened;
- Subjects enrolled in the study;
- Subjects who completed the study (or did not with associated reasons);
- Subjects who discontinued the study drug, including atogepant and ubrogepant;
- Subjects who took at least one dose of study drug during the open-label atogepant treatment period (Safety Population 1);
- Subjects who completed open-label atogepant treatment period;
- Subjects who took at least one dose of study drug, either atogepant or ubrogepant, during the open-label atogepant + ubrogepant treatment period (Safety Population 2);
- Subjects who completed open-label atogepant + ubrogepant treatment period;
- Subjects who prematurely discontinued the open-label atogepant treatment period (including reasons for premature discontinuation);
- Subjects who prematurely discontinued the open-label atogepant + ubrogepant treatment period (including reasons for premature discontinuation);
- Subjects who prematurely discontinued the study (including reasons for premature discontinuation);
- Subjects in the mITT 1 Population;
- Subjects in the mITT 2 Population.

Screen failure subjects (i.e., subjects who consented to participate in the study but were not enrolled) and the associated reasons for failure to enroll will be summarized and listed for all screened subjects.

The summary of subject accountability by investigator also will include the number of subjects who enrolled in the study, completed the study, discontinued study drug, and

subjects in the mITT 1, mITT 2, Safety Population 1, and Safety Population 2, respectively.

6.0 Study Treatment Duration and Compliance

Duration of treatment for atogepant, defined for each subject as last dose date minus first dose date + 1, will be summarized for the Safety Population 1 and Safety Population 2. Duration of treatment for atogepant will be summarized for each period (open-label atogepant period or open-label atogepant + ubrogepant period) and the entire open-label period using the number of subjects treated, mean, standard deviation, median, minimum and maximum. In addition, the number and percentage of subjects in each treatment duration of ≥ 1 day, ≥ 7 days, ≥ 14 days, ≥ 21 days, ≥ 28 days, ≥ 35 days, ≥ 42 days, ≥ 49 days, ≥ 56 days, ≥ 63 days, ≥ 70 days, ≥ 77 days, ≥ 84 days, ≥ 91 days, ≥ 98 days, ≥ 105 days, ≥ 112 days, ≥ 119 days, ≥ 126 days, ≥ 133 days, ≥ 140 days, ≥ 147 days, ≥ 154 days, ≥ 161 days, ≥ 168 days will be summarized.

Duration of treatment for ubrogepant, defined as the number of doses and days of ubrogepant taken, will be summarized for the Safety Population 2, by the number of subjects treated, mean, standard deviation, median, minimum and maximum.

Treatment compliance of atogepant for a specific period (open-label atogepant period and open-label atogepant + ubrogepant period) is defined as the number of atogepant doses actually taken by a subject during that period divided by the number of atogepant doses that were expected to be taken during the same period multiplied by 100. Percent treatment compliance will be summarized in each period for the Safety Population 1 and Safety Population 2.

Ubrogepant is taken as needed, so no treatment compliance will be provided for ubrogepant.

7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

7.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the Safety Population 1 and 2. Continuous demographic variables include age, weight, height, and body mass index (BMI). Categorical demographic variables include sex, ethnicity (Hispanic or Latino, Not Hispanic or Latino), race, race group (White, All Other Races), BMI group (< 25, 25-30, and ≥ 30), and age group (< 20, 20-29, 30-39, 40-49, 50-59, 60-69, and ≥ 70).

Disease characteristics are contained in migraine history, including diagnosis, duration of disorder, migraine prevention medication in the past, average number of migraine and headache days per month at baseline and in the last 3 months, and acute medications taken to treat migraine headaches.

Categorical variables will be summarized with the number and percentage of subjects; percentage will be calculated based on the non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, Q1, Q3, minimum, and maximum).

7.2 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of subjects in each medical history category (by MedDRA system organ class and preferred term) will be summarized. The system organ class (SOC) will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term). Migraine history will be summarized separately according to eCRF.

7.3 Prior and Concomitant Medications

Prior and concomitant medications will be summarized separately by generic name. The number and percentage of subjects taking prior and concomitant medications will be summarized by generic name. Concomitant medication will be summarized for each open-label period and overall. A prior medication is defined as any medication taken prior to the date of the first dose of study drug.

A concomitant medication in the open-label atogepant treatment period (Period 1) is defined as any medication that started prior to the date of the first dose of study drug and continue to be taken after the first dose of study drug or any medication that started on or after the date of the first dose of study drug, but not after the date of the last dose of study drug in Period 1 plus 30 days (if subject discontinued from study drug in Period 1) or Visit 5 whichever comes later.

A concomitant medication in the open-label atogepant + ubrogepant treatment period (Period 2) is defined as any medication that started prior to the date of the first dose of study drug in Period 2 and continue to be taken after the first dose of study drug in Period 2 or any medication that started on or after the date of the first dose of study drug in Period 2, but not after the date of the last dose of study drug plus 30 days or Visit 9 whichever comes later.

The number and percentage of subjects taking medications will be summarized by generic drug name based on the World Health Organization (WHO) Drug Dictionary Enhanced for both prior and concomitant medications.

8.0 Handling of Potential Intercurrent Events for the Primary and Secondary Endpoints

The efficacy endpoints are exploratory, so no handling of intercurrent events for efficacy endpoints will be provided.

9.0 Efficacy Analyses

9.1 General Considerations

All efficacy analyses will be conducted in the mITT 1 or mITT 2 Population.

9.2 Handling of Missing Data

Descriptive statistics for efficacy endpoints will be based on observed cases (OC) only. Missing data will be handled using mixed model for repeated measures (MMRM) without imputation for the efficacy analysis for continuous endpoints unless specified otherwise.

9.3 Exploratory Efficacy Endpoint(s) and Analyses

9.3.1 Exploratory Efficacy Endpoint(s)

The exploratory efficacy endpoints are listed in Section 3.2.

9.3.2 Analysis of Exploratory Efficacy Endpoints

Continuous Endpoints

The change from baseline in mean monthly migraine days, headache days, and acute medication use days across Weeks 1 to 12, Weeks 13 to 24, and at each 4-week interval will be analyzed using a mixed-effect model for repeated measures (MMRM) for each period (open-label atogepant period or open-label atogepant + ubrogepant period), including visit as a categorical fixed effect, and baseline value and baseline-by-visit interaction as covariates. An unstructured covariance matrix will be used to model the covariance of within-subject repeated measurements. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The analysis will be performed based on postbaseline values using only the observed cases without imputation of missing values. Contrasts will be constructed to obtain the average treatment effects across the 12-week period for Weeks 1 to 12 or Weeks 13 to 24. The treatment effect (across the 12-week period for Weeks 1 to 12 or Weeks 13 to 24, and at each 4-week

interval) will be estimated by the least square (LS) Means, the standard error (SE) and 95% confidence intervals.

(HIT)-6 total score is derived as specified in the Appendix A. The change from baseline for (HIT)-6 total score will be analyzed similarly as above using MMRM.

The percent work time missed, percent impairment while working, percent overall impairment, and percent activity impairment due to migraine at Weeks 4, 8, 12, 16, 20, and 24 as assessed by the Work Productivity and Activity Impairment Questionnaire: Migraine (WPAI:MIGRAINE) are derived as specified in Appendix A. The change from baseline for these endpoints will be analyzed similarly as above using MMRM.

MSQ Role Function-Preventive domain score, Role Function-Restrictive domain score and Emotional Function domain score are derived as specified in Appendix A. The change from baseline for these endpoints will be analyzed similarly as above using MMRM.

(PHQ)-4 score is derived as specified in Appendix A. The change from baseline for (PHQ)-4 will be analyzed similarly as above using MMRM.

The MTOQ-6 score is derived as specified in Appendix A. The MTOQ-6 score will be summarized by visit.

Percentages of migraine attacks treated with ubrogepant that result in pain freedom at 2 hours, pain relief at 2 hours, sustained pain freedom from 2 to 24 hours, and sustained pain relief from 2 to 24 hours across Weeks 13 to 24 and at each 4-week interval will be summarized using descriptive statistics.

Binary or Categorical Endpoints

The responders are defined as subjects with at least 25%, 50%, 75%, and 100% reduction compared to baseline in mean monthly migraine days across Weeks 1 to 12, Weeks 13 to 24, and at each 4-week interval. They will be summarized using descriptive statistics.

Patient satisfaction with atogepant, ubrogepant, and concomitant use of atogepant and ubrogepant are categorized as extremely satisfied, satisfied, slightly satisfied, neither satisfied nor dissatisfied, slightly dissatisfied, dissatisfied, and extremely dissatisfied. The proportions of patient satisfaction responders, defined as subjects who are satisfied or extremely satisfied with the study treatment for migraine prevention, will be summarized using descriptive statistics by visits.

Proportions of subjects with at least a 5-point improvement (decrease) from baseline in HIT-6 total score at Weeks 4, 8, 12, 16, 20, and 24 will be summarized using descriptive statistics.

Proportions of subjects with PGIC of "much better" or "very much better" at Week 12 (atogepant) and Week 24 (atogepant + ubrogepant) will be summarized.

9.4 Efficacy Subgroup Analyses

For the efficacy endpoint, change from baseline in mean monthly migraine days, headache days, and acute medication use days, subgroup analyses will be performed by ubrogepant usage subgroups.

Two subgroups will be applied in subgroup analyses for subjects who took ubrogepant:

Subgroups by number of ubrogepant use days:

- Never used ubrogepant
- Low ubrogepant use: 1-3 days of ubrogepant taken in the atogepant + ubrogepant treatment period
- Moderate ubrogepant use: 4-9 days of ubrogepant taken in the atogepant + ubrogepant treatment period
- High ubrogepant use: >=10 days of ubrogepant taken in the atogepant + ubrogepant treatment period

Subgroup by number of ubrogepant doses taken:

- Never used ubrogepant
- Low ubrogepant use: 1-6 doses of ubrogepant taken in the atogepant + ubrogepant treatment period
- Moderate ubrogepant use: 7-18 doses of ubrogepant taken in the atogepant + ubrogepant treatment period
- High ubrogepant use: 19+ doses of ubrogepant taken in the atogepant + ubrogepant treatment period

For each subgroup analysis, summary statistics will be provided, including mean and standard deviation, minimum, maximum, and 95% CI for baseline and change from baseline across Weeks 13-24.

10.0 Safety Analyses

10.1 General Considerations

The safety analyses will be performed using the Safety Population 1 or 2. The safety endpoints include AEs, clinical laboratory evaluations, vital sign measurements, ECG parameters, the C-SSRS, and pregnancy test. For each of the clinical laboratory, vital sign, and ECG parameters, the last non-missing safety assessment before the first dose of study drug will be used as the baseline for all analyses of that safety parameter.

Continuous variables will be summarized by the number of subjects, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum values. Categorical variables will be summarized by number and percentage of subjects.

10.2 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA System Organ Class (SOCs) and preferred terms (PTs) according to the version of MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study

report. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational products will be reported.

10.2.1 Treatment-Emergent Adverse Events

Treatment-emergent AEs are defined as any AE with the onset that is after the first dose of study drug. Events when the onset date is the same as the study drug start date are assumed to be treatment-emergent. An AE that occurs more than 30 days after the last dose of open-label study treatment or Visit 8 whichever comes later will not be counted as a TEAE.

The number and percentage of subjects experiencing treatment-emergent AEs will be summarized by the open-label atogepant treatment period, the open-label concomitant atogepant + ubrogepant treatment period, and the entire treatment period.

TEAEs that started after the date of last dose of study treatment will be considered as newly emergent. The number and percentage of subjects reporting newly emergent TEAEs will be summarized by system organ class and preferred term.

10.2.2 Adverse Event Overview

An overall of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any treatment-emergent AE
- Any treatment-emergent AE related to study drugs (atogepant and ubrogepant) according to the investigator
- Any severe treatment-emergent AE
- Any serious treatment-emergent AE
- Any treatment-emergent AE leading to discontinuation of study drugs (atogepant and ubrogepant)

- Any treatment-emergent AE leading to death
- All deaths

10.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

Treatment-emergent adverse events will be summarized, for each treatment period and overall, by SOC and PT; by maximum relationship to study drug as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by maximum severity and SOC and PT. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

The incidence of common (≥ 2% and ≥ 5% [after rounding] of subjects) TEAEs will be summarized by preferred term for each treatment period and overall.

Kaplan-Meier Curves will be provided for the time to the occurrence of certain AEs (nausea, constipation, fatigue/somnolence, decrease appetite) for the entire open-label treatment period.

10.2.4 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

The number and percentage of subjects in the Safety Population 1 and Safety Population 2 who have SAEs (including deaths) and AEs leading to study drug discontinuation will be summarized by SOC and PT.

In addition, the list for SAEs (including deaths) and AEs leading to study intervention discontinuation will provided.

10.2.5 Adverse Events of Special Interest

All AEs of special interest must be reported within 24 hours of the time the investigator becomes aware of the event using the AE eCRF and the hepatic eCRF.

The following AEs of special interest will be monitored during the study:

- Treatment-emergent elevated ALT or AST laboratory value ≥ 3 × ULN.
- Potential Hy's law cases: elevated ALT or AST laboratory value ≥ 3 × ULN and an elevated total bilirubin laboratory value ≥ 2 × ULN and, at the same time, an alkaline phosphatase laboratory value < 2 × ULN.

10.3 Laboratory Data

Data collected from central laboratories, including additional laboratory testing due to an SAE, will be used in all analyses, except for Baseline where SAE-related laboratory assessments on or before the first dose of study drug without timestamp will be excluded. The details for SAE-related laboratory baseline can be found in the SPP. The clinical laboratory tests defined in the protocol (e.g., hematology, clinical chemistry and urinalysis) will be summarized.

Each laboratory variable will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, Q1, Q3, minimum and maximum. Mean change from baseline to each applicable post-baseline visit will be summarized with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard deviation, median, Q1, Q3, minimum and maximum will be presented for the mean change from baseline. In addition, descriptive statistics for values and changes from the baseline values in conventional units at each assessment time point will be presented for selected clinical laboratory parameters listed in Appendix D. A description of reporting the lab values in conventional units in patient narratives (along with the standard reporting in SI units) is presented at the end of Appendix D.

Changes in laboratory parameters will be summarized using shift tables categorized as low, normal, or high based on the normal ranges of the laboratory used for each sample. A shift table will be provided to summarize shifts from baseline to the final post-baseline value for all lab categories.

Laboratory abnormalities will be evaluated based on potentially clinically significant (PCS) criteria (Table 4). For each laboratory PCS criterion, the number and percentage of subjects who have a laboratory value meeting the criteria will be summarized in Safety Populations 1 and 2 for each treatment period and overall. Listings will be provided to summarize subject-level laboratory data for subjects meeting PCS criteria.

The number and percentage of subjects meeting each of the criteria for postbaseline hepatic laboratory abnormalities listed in Table 5 will be summarized. The percentages will be calculated relative to the number of subjects with at least 1 available postbaseline assessment. The numerator will be the total number of subjects having at least 1 postbaseline value that meets the specific category during the study. A supportive listing will also be provided.

The number and percentage of subjects with an adjudicated case (i.e., ALT ≥ 3 x ULN and/or AST ≥ 3 x ULN) will be summarized by relationship of ALT or AST elevation to study medication. The percentages will be calculated relative to the number of subjects with at least 1 adjudicated case. The numerator will be the number of subjects with at least 1 adjudicated case in the specific category of relationship. If a subject has more than 1 adjudicated case, he or she will be counted in the most relevant category of relationship.

Subjects with an adjudicated case (i.e., ALT ≥ 3 x ULN or AST ≥ 3 x ULN) will be listed with their ALT and AST assessments, adjudication dates, relationship of ALT or AST elevation to study medication, and confounding factor(s). Additional listings will be provided for subjects who meet ALT ≥ 3 x ULN or AST ≥ 3 x ULN and/or potential Hy's law and have one of the following categories: at least 1 abnormal liver biochemistry risk factor, at least 1 liver disease sign and symptom, at least 1 liver diagnostic test performed, consultation with a specialist for liver evaluation, liver lab tests performed, and drug screen performed, respectively.

Potential Hy's Law criteria within a 24-hour window is defined by a postbaseline evaluation of alanime aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 x ULN, along with total bilirubin (TBL) ≥ 2 x ULN and a non-elevated alkaline

phosphatase (ALP) < 2 x ULN, all based on blood draws collected within a 24-hour period. Patients who meet the potential Hy's Law criteria will be summarized. Supportive listing will also be provided.

A listing of urine pregnancy test results will be provided for female subjects of child-bearing potential with at least one positive result.

10.4 Vital Signs

Vital sign measurements of systolic and diastolic blood pressures (sitting and standing), pulse rate (sitting and standing), respiratory rate, temperature, weight, orthostatic systolic blood pressure, orthostatic diastolic blood pressure, and orthostatic pulse rate will be summarized on Safety Populations 1 and 2.

Each vital sign variable will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, Q1, Q3, minimum and maximum. Mean change from baseline to each applicable post-baseline visit will be summarized for each vital sign variable, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard deviation, median, Q1, Q3, minimum and maximum will also be presented.

Vital sign variables will be evaluated based on PCS criteria (Table 6). For each vital sign PCS criterion, the number and percentage of subjects who have a vital sign value meeting the criteria will be summarized. Listings will be provided to summarize subject-level vital sign data for subjects meeting PCS criteria.

10.5 Other Safety Analyses

10.5.1 Electrocardiogram

Descriptive statistics for ECG parameters (i.e., heart rate, PR interval, QRS interval, RR interval, QT interval, and QTc interval) at baseline, postbaseline, and changes from baseline values at each postbaseline timepoint will be presented for the Safety Populations 1 and 2.

ECG parameter values are considered PCS if ECG values meet either the actual value or change from baseline PCS high criteria listed in Table 7. The number and percentage of subjects with PCS postbaseline values will be summarized. The percentages will be calculated relative to the number of subjects with an available non-PCS baseline value and at least 1 postbaseline assessment. The numerator will be the total number of subjects with an available non-PCS baseline value and at least 1 PCS postbaseline ECG value during the study. A supportive listing of subjects with PCS postbaseline values will be provided. A listing of all AEs for participants with PCS ECG values will also be provided.

The number and percentage of subjects meeting each of the criteria for postbaseline ECG values of clinical interest listed in Table 5 will be summarized. Subjects will be counted only once for the most severe category. A supportive listing of participants with postbaseline QTcF increases > 30 msec will be provided, including the PID number, study center, and all QTc values (including changes from baseline). A listing of all AEs for participants with postbaseline QTcF increases > 30 msec will also be provided.

A shift table from baseline to the end of open-label treatment period in the investigator's overall interpretation of the ECG will be presented for the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant. A tabular display of subjects with postbaseline clinically significant ECG abnormalities according to the investigator's overall interpretation will be provided.

10.5.2 Columbia-Suicide Severity Rating Scale

For C-SSRS, the number and percentage of subjects with suicidal ideation or suicidal behavior as recorded on the C-SSRS will be summarized for the Safety Populations 1 and 2. The distribution of responses for most severe suicidal ideation and most severe suicidal behavior in the subject's lifetime history, in the past 6 months, in the open-label treatment period (atogepant treatment period, atogepant + ubrogepant treatment period, and overall), and in the follow-up period will also be presented. Supportive listings will be provided and will include the PID number, study center number, lifetime history, and postbaseline

values. Intensity of suicidal ideation and suicidal behavior type will also be included in these listings.

10.6 Safety Subgroup Analyses

Two subgroups will be applied in subgroup analyses based on subjects' ubrogepant use:

Subgroup by number of ubrogepant use days:

- Never used ubrogepant
- Low ubrogepant use: 1-3 days of ubrogepant taken in the atogepant + ubrogepant treatment period
- Moderate ubrogepant use: 4-9 days of ubrogepant taken in the atogepant + ubrogepant treatment period
- High ubrogepant use: >=10 days of ubrogepant taken in the atogepant + ubrogepant treatment period

Subgroup by number of ubrogepant doses taken:

- Never used ubrogepant
- Low ubrogepant use: 1-6 doses of ubrogepant taken in the atogepant +ubrogepant treatment period
- Moderate ubrogepant use: 7-18 doses of ubrogepant taken in the atogepant + ubrogepant treatment period
- High ubrogepant use: 19+ doses of ubrogepant taken in the atogepant + ubrogepant treatment period

TEAE, serious TEAE, and TEAE leading to study drug discontinuation will be summarized by subgroups.

11.0 Interim Analyses

An interim analysis that includes all safety and efficacy analyses is planned when at least 30 subjects have completed Visit 8 to support access/reimbursement negotiations.

11.1 Data Monitoring Committee

An independent DMC will be established to review unblinded safety data and summary reports, identify any safety issues and trends, and make recommendations to AbbVie, including ongoing trial conduct or modifications to the trial, if emerging data show unexpected and clinically significant AEs of treatment.

Details of the DMC memberships, standard operational procedures for data monitoring/review, frequency of review, and other pertinent details will be provided in a separate DMC Charter.

12.0 Overall Type-I Error Control

No multiplicity adjustment for overall Type-I Error Control is planned for this study.

13.0 COVID-19 Related Analyses

This section specifies analyses related to COVID-19 pandemic from the following aspects:

- Disposition
- Study visits and study procedures
- Protocol deviation
- Treatment interruption due to COVID-19
- TEAEs related with COVID-19 and supplemental signs and symptoms
- COVID-19 status (COVID-19 testing results or contact with a COVID-19 positive person)
- COVID-19 vaccination

The Safety Populations 1 and 2 will be used for the planned analyses described above. The number of subjects with study visits impacted by COVID-19 will be summarized. In addition, the number of subjects impacted by COVID-19 and their corresponding

disposition status in the open-label periods and the follow-up period will be summarized respectively.

The number of subjects who missed at least one entire visit, had in person, partial assessment done, and had virtual visits due to COVID-19 will be summarized.

The number of subjects with protocol deviation due to COVID-19 will be provided. The number of subjects with study drug interruption due to COVID-19 will be provided as well. The number of subjects with TEAEs and serious TEAEs related to COVID-19 vaccine will be provided.

Supporting listings for the described analyses above and TEAEs leading to study discontinuation related to COVID-19 will be provided.

14.0 Version History

This Statistical Analysis Plan (SAP) for Study M23-072 is based on the protocol dated 22July2022.

Table 1. SAP Version History Summary

Version	Date	Summary
1.0	31 March 2022	Initial version
2.0	07 December 2022	Corrected typos and removed duplicated paragraphs throughout the document. Changed "double-blind" to "open-label" throughout the document. Updated language throughout the document to align with protocol. Section 2.3 changed Week 1 to Day 1 to be consistent with protocol. Section 3.2 changed Weeks 12 to Weeks 13 to avoid overlap of visits. Section 5.0 deleted 'Participants enrolled (randomized) in the study'. Section 5.0 changed 'follow-up period' to 'study' to correct the analysis of discontinuation period. Section 9.3.2 deleted 'and the p-value'. No need to provide p-value in efficacy analyses for this open-label study.

Version	Date	Summary
		Added ubrogepant take dose subgroup definition in Section 9.4 Removed MMRM model-based analysis for under subgroup analysis for Section 9.4. Removed analysis in AESI section as it's covered in Section 10.3. Added subgroup analysis for safety (Section 10.6). Updated Appendix A to clarify MTOQ6's definition. Updated Appendix B, protocol deviation section to align with standard. Removed Appendix C as AESIs are defined in the SAP body. Updated Appendix index accordingly. Updated mITT 1 and mITT 2 population definitions with "received" instead of "receive" in Section 4.0. Added that baseline analyses are done for both Safety Population 1 and Safety Population 2 in Section 4.0. Reorganized the subject categories in Section 5.0. Deleted analyses description that were repeated. Added subject accountability by investigator in Section 5.0. Clarified definition for duration of treatment for both atogepant and ubrogepant and the analysis populations in Section 6.0. Specified demographic groups in Section 7.1. Added "migraine prevention medication in the past" to disease characteristics (migraine history) in Section 7.1. Added definitions for concomitant medication for each period in Section 7.3. Updated in Section 9.2 that efficacy analyses are based on observed case (OC). Clarified the meaning of patient satisfaction responder in Section 9.3.2. In Section 9.4, added details about efficacy subgroup analyses and the analysis populations. Deleted MedDRA version in Section 10.2.1 as it's repeated. Specified that study drug include atogepant and ubrogepant in Section 10.2.2. Added analyses detail for Section 10.2.3 (TEAE by SOC & PT), Section 10.2.4 (SAE & AE leading to study drug discontinuation), and Section 10.3 (laboratory data). Clarified potential Hy's law analysis in Section 10.3 For Section 13.0, deleted efficacy evaluation under COVID-19 related analyses, specified the analysis populations, added TEAE leading to study discontinuation related to COVID-19.

Version	Date	Summary
		Moved ECG post-baseline values of clinical interest to appendix Table 8 (newly added). Changed the table numbering accordingly.

15.0 References

1. D'Antona L, Matharu M. Identifying and managing refractory migraine: barriers and opportunities? J Headache Pain. 2019;20(1):89.
2. Fischer MJ. The role of calcitonin gene-related peptide (CGRP) in the pathogenesis of primary headache. Drugs Fut. 2006;31(2):175-81.
3. Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics. 1997;53(3):983-97.
4. Ho TW, Connor KM, Zhang Y, et al. Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention. Neurology. 2014;83(11):958-66.
5. Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics. 1997;53(3):983-97.
6. Pellesi L, Do TP, Ashina H, et al. Dual Therapy With Anti-CGRP Monoclonal Antibodies and Botulinum Toxin for Migraine Prevention: Is There a Rationale? Headache. 2020;60(6):1056-65.

Appendix A. Derivation of Efficacy Variables

A.1 Derivation of Health Outcome Endpoints

MSQ Related Endpoints Derivation

MSQ v2.1 consists of 14 items with a 4-week recall period. The scoring of the MSQ is completed in following 3 steps.

Step 1: Final item value assignment.

Precoded item values and final item values for each MSQ item response are shown in Table 2.

Table 2. Item Values for MSQ Item Responses

Response Categories	Precoded Item Value	Final Item Value
None of the time	1	6
A little bit of the time	2	5
Some of the time	3	4
A good bit of the time	4	3
Most of the time	5	2
All of the time	6	1

Step 2: Computation of raw domain (dimension) scores

Once a final item value has been assigned to each item, a raw score can be computed for each MSQ domain. Role Function Restrictive domain includes Items 1 - 7, Role Function Preventive domain includes Items 8 - 11, and Emotional Function domain includes Items 12 - 14. The raw score for each domain is the algebraic sum of the final item values for all items in that domain.

Missing data handling: if a respondent answered at least half of the items in a domain (or half plus one in the case of scales with an odd number of items), a

missing item value can be estimated using the average of the other completed items within the same dimension.

In detail, for MSQ v2.1 Role Function Restrictive domain, the 7 individual item responses using final item value will be summed, resulting in the raw domain score ranging from 7 to 42 with higher scores indicating better quality of life. If there are missing item responses, the raw domain score will be calculated by summing the non-missing item responses using final item value and dividing by the number of non-missing items and then multiplying by 7 provided that 4 or more items in the domain are completed; otherwise it will be set to missing. For MSQ v2.1 Role Function Preventive and Emotional domains, the raw domain scores will be calculated similarly using final item value respectively. If there are missing item responses, the corresponding raw domain score will be calculated by summing the non-missing item responses using final item value and dividing by the number of non-missing items and then multiplying by the number of questions in that domain provided that 2 or more domain items are completed; otherwise it will be set to missing.

Step 3: Linear transformation to a 0 to 100 scale.

The transformation formula for each MSQ 2.1 domain is listed below

- Role Function -Restrictive: $\frac{(raw\ score-7)*100}{35}$
- Role Function-Preventive: $\frac{(raw\ score-4)*100}{20}$
- Emotional Function: $\frac{(raw\ score-3)*100}{15}$

HIT-6 Total Score Derivation

For HIT-6 total score, pre-coded item values and final item values for each item response are shown in Table 3. Total score is calculated by summing 6 sub-item responses, resulting in the total score ranging from 36 to 78 with higher scores indicating greater impact. If any sub item is missing, then total score will be missing.

Table 3. Item Values for HIT-6 Item Responses

Response Categories	Precoded Item Value	Final Item Value
Never	0	6
Rarely	1	8
Sometimes	2	10
Very Often	3	11
Always	4	13

The HIT-6 instrument has a recall period of 4 weeks for 3 of the 6 items.

Patient Health Questionnaire (PHQ-4)

The PHQ-4 is a 4-item patient health questionnaire for anxiety and depression. Subjects are asked to indicate the frequency with which they have been bothered by 4 symptoms of depressive disorders over the previous 2 weeks, on a 4-point scale: 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day). The total score ranges from 0 to 12 (from best to worst). A Total Score will be calculated using (sum of non-missing items) × 4 /(number of non-missing items) if 3 or more items scores have non-missing responses.

MTOQ 6 Score Derivation

The MTOQ-6 is a 6 question, Likert-type, self-reporting questionnaire with responses ranging from "never" to "half the time or more" with the following response scores: Never = 1, Rarely = 2, Less Than Half The Time = 3, Half The Time Or More = 4. The total score for the MTOQ-6 is the sum of each response score and will be treated as missing if the response is missing for one or more questions.

WPAI:MIGRAINE Related Endpoints Derivation

WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes, as follows:

Questions:

- Q1 = currently employed (working for pay).
- Q2 = missed work hours because of problems associated with your migraine
- Q3 = missed work hours due to other reason.
- Q4 = hours actually worked.
- Q5 = migraine affected productivity while working.
- Q6 = migraine affected regular daily activity.

Scores:

Multiply scores by 100 to express in percentages.

- Percent work time missed due to migraine (absenteeism): Q2/(Q2 + Q4)
- Percent impairment while working due to migraine (presenteeism): Q5/10
- Percent overall work impairment due to migraine (overall work productivity loss): Q2/(Q2 + Q4) + (1- (Q2/(Q2 + Q4))) × (Q5/10)
- Percent activity impairment due to migraine (regular activity impairment): Q6/10

If the response to Q1 ("Currently employed?") is No or missing, absenteeism, presenteeism, and overall work productivity loss will all be set to missing.

Appendix B. Protocol Deviations

The number and percentage of subjects who reported at least one of the following protocol deviation categories will be provided for the Safety Population 1.

- Subject entered into the study even though s/he did not satisfy entry criteria.
- Subject developed withdrawal criteria during the study and was not withdrawn.
- Subject received wrong treatment or incorrect dose of study.
- Subject took prohibited concomitant medication.

Appendix C. Potentially Clinically Significant Criteria for Safety

The potentially clinically significant criteria for clinical laboratory parameters, vital signs and ECG parameters are provided in the following tables.

Clinical laboratory parameters are provided in the following tables.

Table 4. Potentially Clinically Significant Criteria for Clinical Laboratory Parameters

Category	Parameter	SI Unit	PCS Criteria	
			PCS Low	PCS High
Chemistry	Albumin	g/L	< 0.8 × LLN	> 1.2 × ULN
	Alanine aminotransferase	U/L	—	≥ 3.0 × ULN
	Alkaline phosphatase	U/L	—	≥ 3.0 × ULN
	Aspartate aminotransferase	U/L	—	≥ 3.0 × ULN
	Bicarbonate	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Bilirubin, total	µmol/L	—	≥ 1.5 × ULN
	Blood urea nitrogen	mmol/L	—	> 1.5 × ULN
	Calcium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Chloride	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Cholesterol, total	mmol/L	—	> 1.6 × ULN
	Creatinine	µmol/L	—	> 1.5 × ULN
	Creatine kinase	U/L	—	> 2.0 × ULN
	Estimated glomerular filtration rate	mL/min/1.73m^2	< 60 mL/min/1.73m^2	—
	Glucose, nonfasting	mmol/L	< 0.8 × LLN	> 2.0 × ULN
	Lactate dehydrogenase (LDH)	U/L	—	> 3.0 × ULN
	Phosphorus	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Potassium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Protein, total	g/L	< 0.9 × LLN	> 1.1 × ULN
	Sodium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Triglycerides	mmol/L	—	> 2.0 × ULN
	Uric acid	µmol/L	—	> 1.2 × ULN

Category	Parameter	SI Unit	PCS Criteria	
			PCS Low	PCS High
Hematology	Basophils, absolute cell count	10^9/L	—	> 2.0 × ULN
	Eosinophils, absolute cell count	10^9/L	—	> 2.0 × ULN
	Hematocrit	Ratio	< 0.9 × LLN	> 1.1 × ULN
	Hemoglobin	g/L	< 0.9 × LLN	> 1.1 × ULN
	Lymphocytes, absolute cell count	10^9/L	< 0.7 × LLN	> 1.3 × ULN
	Monocytes, absolute cell count	10^9/L	< 0.5 × LLN	> 2.0 × ULN
	Neutrophils, absolute cell count	10^9/L	< 0.7 × LLN	> 1.3 × ULN
	Platelet count	10^9/L	< 0.5 × LLN	> 1.5 × ULN
	Red blood cell count	10^{12}/L	< 0.9 × LLN	> 1.1 × ULN
	White blood cell count	10^9/L	< 0.9 × LLN	> 1.5 × ULN
Urinalysis	pH	pH	< 0.9 × LLN	> 1.1 × ULN
	Glucose	mmol/L	—	Positive[1]
	Protein	g/L	—	Positive[2]
	Specific gravity	—	—	> 1.1 × ULN

LLN = lower limit of normal value; ULN = upper limit of normal value; normal value provided by laboratory; SI = Le Système International d'Unités (International System of Units)

1. Any results other than negative will be considered as positive.
2. Any results other than trace or negative will be considered as positive.

Table 5. Criteria for Hepatic Laboratory Abnormalities

Laboratory Parameter	Categories
ALT	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN

Laboratory Parameter	Categories
AST	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
ALT or AST	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
Bilirubin Total	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
Alkaline Phosphatase	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
Concurrent Elevations[1]	ALT or AST ≥ 3 × ULN and Bilirubin Total ≥ 1.5 × ULN
	ALT or AST ≥ 3 × ULN and Bilirubin Total ≥ 2 × ULN
Potential Hy's Law[1]	ALT or AST ≥ 3 × ULN and Bilirubin Total ≥ 2 × ULN and ALP < 2 × ULN

ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ALP = alkaline phosphatase; ULN = upper limit of normal (value provided by the laboratory)

1. Elevations are from the same day.

Vital sign values will be considered PCS if they meet both the observed value criterion and the change from baseline value criterion, if both criteria are available, or meet either the observed value criterion or the change from baseline value criterion that is detailed in the following table.

Table 6. Potentially Clinically Significant Criteria for Vital Signs Parameters

Parameter	Flag	Criteria	
		Observed Value	Change from Baseline
Systolic blood pressure, mm Hg	High	≥ 180	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Diastolic blood pressure, mm Hg	High	≥ 105	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Pulse rate, bpm	High	≥ 120	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Weight, kg	High	—	Increase of ≥ 7%
	Low	—	Decrease of ≥ 7%
Orthostatic SBP change, mm Hg	Low	≤ -20	—
Orthostatic DBP change, mm Hg	Low	≤ -15	—
Orthostatic Pulse rate change, bpm	High	≥ 25	—

SBP = Systolic blood pressure; DBP = Diastolic blood pressure; bpm = beats per minute

ECG parameter values are considered PCS if ECG values meet either the actual value or change from baseline PCS high criteria listed in the following table.

Table 7. Potentially Clinically Significant Criteria for ECG Parameters

Parameter	Unit	Criterion
QRS interval	msec	≥ 150
PR interval	msec	≥ 250
QTc (QTcB or QTcF) interval	msec	> 500
QTc (QTcB or QTcF) interval	msec	Increase from baseline > 60

Table 8. ECG Post-baseline Values of Clinical Interest

Parameter	Unit	Criterion
QTcF interval	msec	> 450
		> 480
		> 500
		Increase > 30 but ≤ 60
		Increase > 60

Appendix D. Laboratory Parameters in Conventional Unit

All clinical laboratory parameters will be reported in the International System (SI) units as standard practice. In addition, descriptive statistics for values and changes from baseline in conventional units at all assessed visits will be reported for selected laboratory parameters as listed in the following table.

Table 9. List of Selected Parameters Reported in Conventional Unit

Number	Laboratory Parameter	Conventional Unit	Decimal Places
1	Alanine Aminotransferase (SGPT)	U/L	0
2	Albumin	g/dL	1
3	Alkaline Phosphatase	U/L	0
4	Aspartate Aminotransferase (SGOT)	U/L	0
5	Bilirubin, Direct (Conjugated)	mg/dL	1
6	Bilirubin, Indirect (Unconjugated)	mg/dL	1
7	Bilirubin, Total	mg/dL	1
8	Blood Urea Nitrogen	mg/dL	0
9	Calcium	mg/dL	1
10	Cholesterol, HDL	mg/dL	0
11	Cholesterol, LDL	mg/dL	0
12	Cholesterol, LDL direct and calculated (combined) *(This lab parameter could be the same as #11)*	mg/dL	0
13	Cholesterol, Total	mg/dL	0
14	Creatine Kinase	U/L	0
15	Creatinine	mg/dL	1
16	Glucose	mg/dL	0
17	Insulin	µIU/mL	1
18	Triglycerides	mg/dL	0
19	Uric Acid	mg/dL	1
20	Hemoglobin	g/dL	1

Patient narratives will also include the values in conventional units for the selected lab parameters in below table. That will be accomplished by presenting the values in conventional units within the parentheses next to the values in SI units.

Table 10. Presenting Laboratory Data Using SI and Conventional Units in Narratives

LABORATORY DATA						
		Normal Range		VISIT01	VISIT05	VISIT07
Lab Test	Test Name	Low	High	2012-07-03	2012-08-07	2012-09-04
CHEMISTRY	Bilirubin, Total (µmol/L (mg/dL))	0 (0)	18.81 (1.1)	6.84 (0.4)	5.13 (0.3)	5.13 (0.3)

Appendix E. List of Abbreviations

Abbreviation/Term	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
C-SSRS	Columbia–Suicide Severity Rating Scale
DSMB	Data Safety Monitoring Board
eCRF	electronic case report form
ECG	electrocardiogram, electrocardiographic
EM	episodic migraine
EOS	end of study
ET	early termination
IWRS	interactive web response system
LLN	lower limit of normal value
LSM	least squares mean
MedDRA	Medication Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed-effects model for repeated measures
PCS	potentially clinically significant
PT	preferred term
Q1	first quartile (25th percentile of the data)
Q3	third quartile (75th percentile of the data)
QD	once daily
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
SAE	serious adverse event
SAP	statistical analysis plan
SI	Le Système International d'Unités (International System of Units)
SOC	standard of care
TBL	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal value
WHO	World Health Organization

Appendix F. Changes to Protocol-planned Analyses

There are no changes from the protocol-planned analyses.